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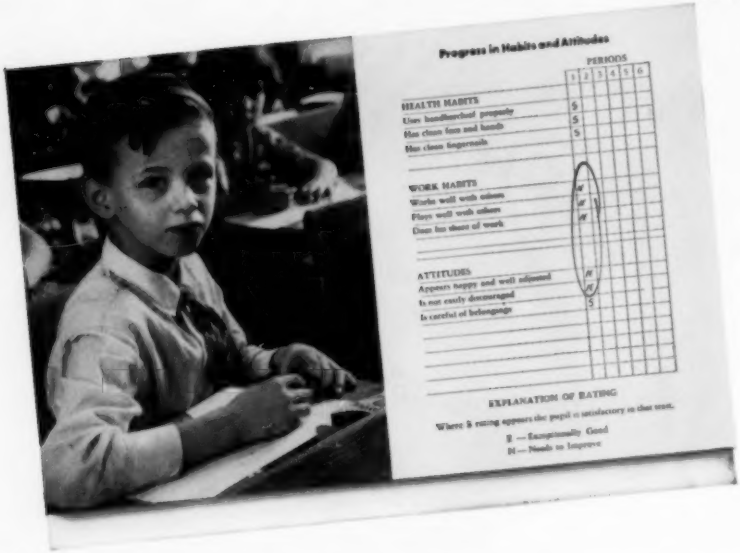

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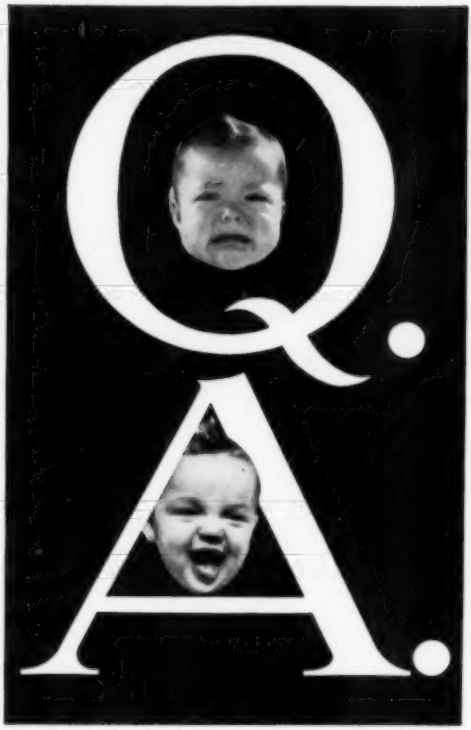

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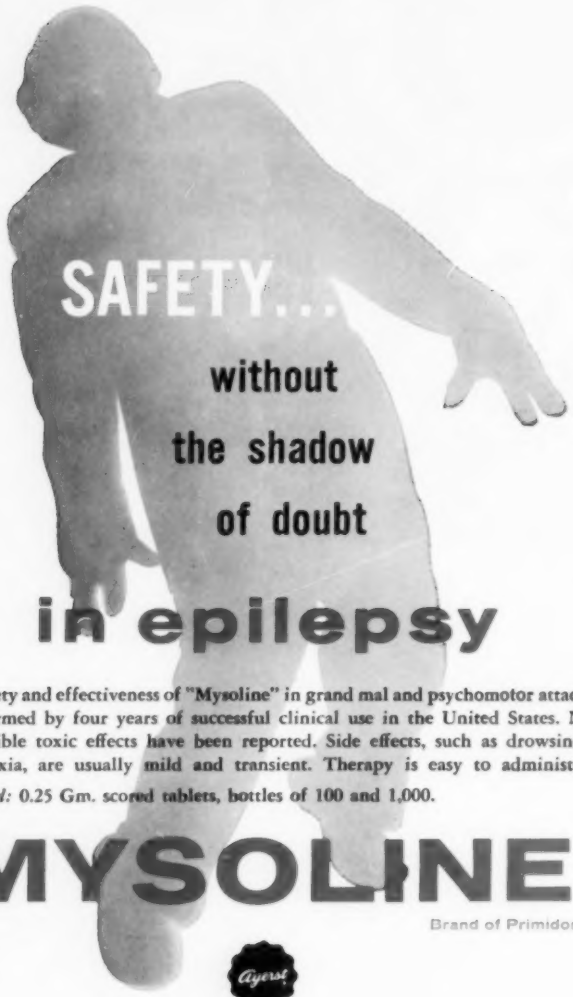

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VENOUS CHANNEL THROMBOSIS AS A POSSIBLE CAUSE OF CEREBRAL PARALYSIS OF EARLY LIFE

CYRIL B. COURVILLE, M.D.*†°

California

In the recent past, numerous studies concerned with gross lesions of the brain apparently responsible for cerebral palsy, mental deficiency and epilepsy have served to focus attention on the birth process as the most likely episode responsible for the production of these lesions. There remains considerable divergence of opinion, however, as to the precise mechanism of production of the various structural alterations in the brain found at autopsy. At first no attempt was made to evaluate these changes in terms of pathogenesis, a dozen or more individual lesions all being considered to be a result of "birth injury." More recently, an attempt has been made to separate from the relatively rare, purely traumatic effects of birth, a group of lesions which obviously demand some other explanation for their occurrence. This is particularly true of alterations suggestively the result of circulatory disorders in general and cerebral anoxia in particular. But even those inclined to accept the circulatory concept as the prime pathogenic factor are divided into three schools of thought, those favoring hemorrhage, those leaning toward ischemia and those believing that venous channel thrombosis is the essential factor in etiology.

The concept of venous thrombosis as a cause of certain groups of lesions of early life including certain cortical alterations, (i.e., nodular cortical atrophy), some degenerative changes in the cerebral white matter, (i.e., cystic degeneration of the cerebral cen-

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† Aided by a grant from the National Institute of Neurological Diseases and Blindness, (# B-1248) Bethesda, Maryland.
° Read before the annual meeting of the American Academy for Cerebral Palsy on September 26, 1958, at Providence, Rhode Island.

trum), as well as a specific disorder of the basal ganglia (i.e., status marmoratus) has deeply entrenched itself in the thinking of many, if not most, of the workers in this field. A brief note on how this concept came into being will serve as an appropriate introduction to the subject.

HISTORY OF VENOUS CHANNEL CONCEPT

It was apparently Gowers[1] who first proposed the theory of the venous thrombosis for the lesions in cases of cerebral palsy. Although he supported the theory of focal meningeal hemorrhage for the paraplegic manifestations of Little's disease, he also pointed out that actual cortical destruction might be a result of thrombosis of the cortical veins. Possibly because his suggestion was not based upon personal observations, the concept of venous thrombosis as a cause for localized cortical atrophy was given little consideration. The idea was resurrected thirty odd years later when Siegmund[2] also postulated the occurrence of porencephalic cysts on the basis of cerebral softening consequent to venous thrombosis. Schwartz[3] and Saenger[4] pointed out that postnatal hemorrhages in the cerebral white matter sometimes occurred in the area drained by the internal cerebral veins. This concept which considered these hemorrhages to be a result of over burdening or actual occlusion of the internal cerebral veins seemed to meet promptly with general acceptance.

Holzer[5] invoked this possibility to account for the distribution of the lesions of status marmoratus in the basal ganglia as have Malamud[6] and Benda[7] more recently. Marburg and Casamajor[8] likewise used this mechanism to explain the presence of a number of gross destructive cerebral lesions of early life, particularly chronic cystic degeneration of the cerebral white matter. The possibliity that even diffuse sclerosis and other demyelinating disorders might have a similar genesis was also entertained. Marburg and his coworkers[9] also supported this venous concept of Schwartz[4] and Siegmund[2] to explain the development of porencephalic cysts. Although Norman[10] has been less enthusiastic about this mechanism in accounting for the pathogenesis of nodular cortical atrophy since he discovered such a case without evidence of sinus thrombosis, his most recent pronouncement on this lesion suggests that he does not eliminate this possibility altogether.

As the years have gone by, the present writer has become less and less inclined to accept the theory of venous channel occlusion as an explanation for these lesions. This was the result of an in-

creasing acquaintance with the structural effects of venous channel thrombosis on one hand and his experiences with the possible effects of cerebral anoxia and ischemia on the other. His observations in the case of cerebral lesions consequent to venous channel thrombosis have revealed a number of facts which do not fit well into this thesis. It therefore seemed worthwhile to him to make a critical review of the entire problem. This study was initiated by making a review of the cerebral lesions incident to venous channel thrombosis as revealed in over 60,000 autopsy protocols. Specific attention was then paid to 52 examples of thrombosis of the superior longitudinal sinus and/or the internal veins of Galen which have been incriminated in the causation of these lesions. Lesions secondary to thrombosis of the superior longitudinal sinus caused by suppurative processes or which were complicated by other infectious lesions were not included for obvious reasons.

To clarify his objectives in this investigation, three fundamental questions have been posed: (1) How often does thrombosis of the superior longitudinal sinus and/or the internal venous system of Galen actually occur as a complication of difficult labor? (2) Does the nature and distribution of the acute cerebral lesions secondary to venous thrombosis suggest a causal relationship to the gross alterations of the brain in early life which are here considered? (3) Does one find in the number and character of the more chronic residuals of venous channel thrombosis any support for the concept of the venous origin of the lesions causing paralysis in early life? Before attempting to answer these questions, a very brief review of the anatomy of venous drainage of the cerebral hemisphere is in order.

VENOUS DRAINAGE OF THE CEREBRAL HEMISPHERES

The cerebral hemispheres are drained of their venous blood by two separate systems, an external and an internal. The *external system* is divided into an anteriobasal complex and a posteriosuperior complex. The second of these complexes, which alone is of concern in this connection, is made up of the superior longitudinal, and, to a much less extent, the inferior longitudinal and straight sinuses and their afferent veins. This system drains the cortex and subcortical white matter of the upper portion of the dorsolateral surface and most of the medial surface of the cerebral hemispheres.

The internal system is composed of two internal cerebral veins (the small veins of Galen and their afferents) which join together

to form the great vein of Galen. This short trunk in turn empties into the straight sinus which lies along the line of juncture of the falx cerebri and the tentorium. This system drains the interior of the cerebral hemispheres including the basal ganglia, the internal capsule and the white matter immediately adjacent thereto (fig. 1). Both the external and internal systems join at the torcular Herophili and the combined current of venous blood are carried away by the lateral and sigmoid sinuses to be emptied into the internal jugular veins.

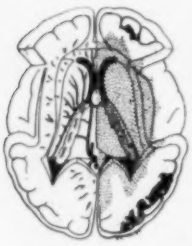

Fig. 1

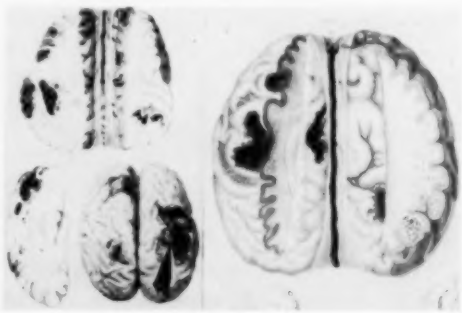

Fig. 2

Fig. 1. Drawing indicating distribution of afferents of internal cerebral veins on left and the area drained by them on the right. (Ehlers and Courville: J. Pediat. 8:619, 1936).

Fig. 2. Examples of cerebral changes after thrombosis of the superior longitudinal sinus as depicted in Cruveilhier's atlas. (Cruveilhier, J.: Anatomie pathologique du corps humaine. J. Baillaire, Paris 1829-1842).

Communications do occur between the external and internal venous systems by way of long anastomotic veins which pass through the cerebral white matter. The dividing line between these two systems is quite variable so that complete occlusion of one venous system, for example, the internal one, tends to result in a very irregular central zone of red softening with ultimate cavitation of this zone. As Schlesinger[11] has pointed out, the internal or Galenic system in particular "is not an anatomical, and much less a functional unit."

HISTORY OF VENOUS CHANNEL THROMBOSIS AND ITS CEREBRAL EFFECTS

Thrombosis of the intracranial venous channels has undoubtedly been seen and perhaps recognized ever since the brain has been

exposed at autopsy. The earliest report of such a case known to the writer was that of Morgagni[12] which, oddly enough, appears to be that of a primary or marantic type of thrombosis of the internal cerebral veins in a woman who died of central cerebral softening after childbirth. It was not until the early decades of the nineteenth century, however, that the structural effects of venous thrombosis on the cerebral tissues came to be fully appreciated. This knowledge was materially promoted by the magnificent lithographs of Cruveilhier[13] (fig. 2). The classical demonstration of the resultant cerebral lesions,

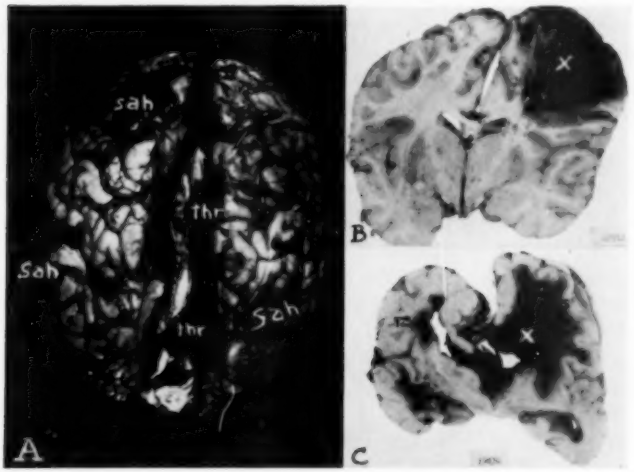

Fig. 3. Cerebral lesions after thrombosis of the superior longitudinal sinus. A. Photograph showing thrombosis within sinus and superior cerebral veins (thr) and multiple foci of subarachnoid hemorrhage (s a h) which surmount individual areas of red softening of the cerebral cortex. B. Cross section of brain showing cortical-subcortical red softening (x) indicates focal hemorrhage. C. Multiple foci of red softening (r s) with gross blood clot in major focus (x).

such as the sharply outlined foci of red softening of the cortex and subcortex, the scattered petechial hemorrhages in both structures, the areas of hemorrhagic softening in the white matter, and the gross hemorrhages into the cerebral centrum were all clearly depicted.

Most of the cases reported during this period were of the secondary or suppurative type. In addition to a number of case reports in the latter part of the nineteenth century, several monographic treatises on venous channel thrombosis, Gerhardt[14]; Hutinel[15]; Halff[16] were published, all of which served to establish this type of vascular disorder as a distinct pathological entity and presented a

comprehensive picture of its cerebral lesions. In this period, a less obvious but very important aspect of the problem, namely, thrombosis of the internal system of veins, also came to be recognized. This particular variety of venous thrombosis was understood to be a result either as an extension into the internal system from a secondary type of dural sinus thrombosis or as a primary lesion incident to inanition and dehydration following diarrhea in infants or to a marked anemia (chlorosis) in adult women. This feature of venous thrombosis has already been reviewed by Ehlers and Courville,[17] and its essential details need not be repeated. With this background it will now be possible to study the possible relation between the birth process and venous channel thrombosis.

FREQUENCY AND SIGNIFICANCE OF POSTNATAL VENOUS CHANNEL THROMBOSIS

When one reads that occlusion of the superior longitudinal sinus and/or the internal system of veins is a "common" consequence of difficult labor, he is naturally prepared to accept the next argument in favor of its causation of gross natal cerebral lesions. This first premise has been assumed by Schwartz[3] (1921, 1924, 1927) in his elaboration of this thesis. His belief that venous stasis or thrombosis is a common sequel at birth is based partly upon a study of a group of cases of early postnatal death reported in the literature, and partly upon his own experience with central cerebral hemorrhages in this period. For example, he refers to the early report of Gerhardt[14] dealing with three cases of sinus thrombosis in infants of 11 days, 3 weeks and 3 months of age. These infants were afflicted with diarrhea (and presumably from resultant dehydration) so it was natural for the author himself to conclude that all these instances of venous thrombosis were of the primary or authochthonous type. As far as can be learned from the report, no significant difficulty in labor had occurred in any of these cases.

Other investigators who have examined postmortem a number of infants who have died at birth or shortly thereafter, have noted what they term a "thrombosis" of the various intracranial venous channels. Such references must therefore be carefully scrutinized. For example, Spencer[18] analyzed the findings at autopsy of 130 stillborn infants or those who died within a few days after delivery. He noted "dark clots" or a "thrombus" in the venous sinuses of four of these infants. In one case (his Case 25) a premature stillborn infant weighing 2 pounds and 13 ounces was born by breech delivery after premature rupture of the bag of waters. A small

amount of hemorrhage was noted under the pericranium and in the basal meninges of the infant. A "black clot" was also found in the superior longitudinal and lateral sinuses. In the second case (Case 97) the infant was born after a natural vertex presentation. The child went into convulsions and died within a few hours after birth. At autopsy, the brain appeared to be congested and edematous and a "thrombus" was found in the superior longitudinal sinus. In the third case (Case 100), the infant survived for 3 days; the brain was intensely congested and a "thrombus" was found in the superior longitudinal sinus. In the fourth case (Case 119), death came after a survival period of 3 days following vertex delivery. A dark clot was found in the dural sinuses. Unfortunately, the details of the "thrombus" are not given in any of these cases so that there must remain a serious doubt as to whether a true antemortem thrombus had actually existed in any instance.

Hamburger (1920)[19] reviewed the findings in 29 cases of venous channel thrombosis in children. The age of the youngest child was 11 days; the exact cause of thrombosis was not stated. Cornwell (1929)[20] made no mention of venous channel thrombosis as a cause of cerebral lesions found at the time of birth in a contribution devoted to this subject.

Fleming and Morten (1930)[21] reviewed a series of 103 cases of postnatal meningeal hemorrhage. Autopsy was performed in 39 instances. What was considered to be thrombus formation in the venous channels was found in 4 cases. In one case, venous channel thrombosis (sinus or veins not named) was associated with hemorrhage into the ventricles in an infant who survived for 3 days. In a second infant who survived for 6 days, ventricular hemorrhage was also associated with thrombosis of the veins of Galen. The child died of pneumonia. In a third infant, with survival for 7 days, thrombosis of the superior longitudinal sinus was considered to be present. The fourth infant survived for 15 days; at autopsy, thrombosis of the meningeal veins was found. Again, the lack of details regarding factors present at the time of birth and the nature of the thrombus, particularly with respect to the clinical background for a possible primary thrombosis, leaves one in considerable doubt as to the origin of any of these occlusions in a true "birth injury."

In Meier's case (1938),[22] a premature infant weighing about 4 pounds (1900 grams) was born spontaneously after a 5 hour labor. Death came after 11 hours. At autopsy, a thrombus was found at the torcular with a minimal extension into the two lateral and the

superior longitudinal sinuses. A small dural hemorrhage was found just anterior to the thrombus. The author expressed the opinion that the sinus may have been irritated by a local compression of the dura by an accessory interparietal bone, but concluded that thrombosis itself was the result of debility.

Zimanyi (1940)[23] reported the case of an infant, normally born, who was noted to be cyanotic on the 11th postnatal day with death occurring on the 17th day of life. At autopsy, an intracranial hemorrhage was the apparent result of thrombosis of both lateral and straight sinuses. The absence of specific information as to occurrence of dystocia as well as the rather long survival period suggests debility as the case of thrombosis in this case.

Arey (1947)[24] made a study of the postmortem findings in 22 premature infants. In two cases a viable infant died on the 14th and 18th postnatal days. "In one infant both lateral sinuses were thrombosed, and in this case there was an associated bronchopneumonia. In the other infant, there were thrombi in the superior [longitudinal] and lateral sinuses and in the great vein of Galen. This infant also showed subarachnoid, intracerebral and intraventricular hemorrhages." There was no indication that labor was particularly difficult in these two cases. The relatively long survival period could well have permitted a primary thrombosis to have occurred. Toomey and Hutt (1949)[25] surveyed 61 cases of thrombosis of the dural sinuses. The youngest child was 3 months old, with otitis media as the obvious cause of thrombosis. No mention was made of a birth injury.

The writer's personal experience at the Los Angeles County Hospital (Courville 1950),[26] may be helpful in this regard. When the autopsy protocols were last reviewed in 1949, 401 cases of death of new born infants were found in a series of 40,000 autopsies. In no case was death attributed to venous channel thrombosis although in many instances the fatal issue was attributed to dystocia.

In this same series of 40,000 autopsies there were two examples of cerebral palsy which were considered clinically to be a possible effect of venous thrombosis. In the first case, that of a mental defective child with spastic paraplegia, no residual evidence of thrombosis of the superior longitudinal sinus was found at time of death *aet* 5 years. A second child of 3 years presented a subtotal chronic cystic degeneration of the cerebral white matter at autopsy, but nothing suggestive of venous channel thrombosis was found. In no fatal case of cerebral palsy, in which the lesion was verified at

autopsy, has there been any reason to suspect venous thrombosis as its cause.

Judging from the experiences of others already cited and assuming that in all these cases a true thrombosis existed, one must agree that a postnatal thrombosis of the intracranial venous channels can and does occasionally occur. A critical inspection of the records in these reported cases seems to indicate, however, that such a thrombosis is not the result of dystocia. Most of these infants were premature and gave evidence of inanition. It seems more reasonable to conclude that postnatal thrombosis of the intracranial venous channels, when it does occur, is primary or autochthonous in character and is not traumatic in etiology.

But what does it matter whether or not postnatal venous thrombosis is traumatic or primary (autochthonous) in etiology? May not such a thrombosis still be the essential cause of the residual lesions in cerebral palsy? We have yet to prove that cerebral residuals of venous thrombosis are not the antecedent lesions of nodular cortical atrophy, of chronic cystic degeneration of the cerebral white matter, or status marmoratus.

SIGNIFICANCE OF NATURE AND DISTRIBUTION OF ACUTE CEREBRAL LESIONS CONSEQUENT TO VENOUS CHANNEL THROMBOSIS

If thrombosis of the superior longitudinal sinus and/or the internal cerebral veins is actually the essential etiological factor in nodular cortical atrophy, chronic cystic degeneration of the cerebral white matter, or status marmoratus, then one should find in the acute lesions resulting from venous thrombosis, some structural resemblances to these chronic states. A search for an answer to the second question is necessary to determine whether or not such analogies do exist. For this purpose, a study was made of all the 53 cases in the writer's series involving a primary thrombosis of the superior cerebral veins, of the superior longitudinal sinus, of the internal cerebral veins, and of some instances of thrombosis of both the superior longitudinal sinuses and the internal venous system. Excluded for obvious reasons are cases of thrombosis of the lateral, cavernous and petrosal sinuses as well as cases of thrombosis of the superior longitudinal sinus and of the internal cerebral veins caused by, or complicated by, suppurative infection.

The types and numbers of the cases which form the basis for the present study are shown in the accompanying table (Table I.)

In this series there were 39 infants of 2 years and under at the time of death, 3 children between 3 and 5 years, and 11 adults

aged 19 to 70. Because there was no essential difference in the nature and distribution of the cerebral lesions in the group of infants and young children as compared to those in the adult group, both were included. In all of the individuals in the infant-early childhood group, venous thrombosis was essentially of the primary or autochthonous type. In the adult group of 11 cases, thrombosis was also primary in 7, while in the other 4, the exciting cause appeared to be syphilis in 2, a septic state in 1, and in another thrombosis of the venous channel was associated with a chronic subdural hematoma.

TABLE I

CASES OF NONSUPPURATIVE VENOUS THROMBOSIS VERIFIED AT AUTOPSY

Thrombosis of superior cerebral veins alone	5 cases
Thrombosis of superior longitudinal sinus & afferent veins (including one case with residual lesions)	25 cases
Thrombosis of the internal venous system of Galen	12 cases
Thrombosis of both the superior longitudinal sinus and internal system of Galen	11 cases
TOTAL	53 cases

In the 5 cases in which only the superior cerebral veins were occluded by a thrombus, the dorsolateral cerebral surface showed only meningocortical congestion in 2, regional subarachnoid hemorrhage in 1, early local cortical softening in 1, and both cortical and subcortical softening in 1.

In the 25 cases of thrombosis of the superior longitudinal sinus, the pattern assumed by the individual lesions were as follows: Hyperemia only of the dorsolateral cerebral surface was present in 4 cases; regional subarachnoid hemorrhage in 2 cases; focal red softening of the cortex in 5 cases (focal frontal in 1 case, focal parietal in 2 cases and multiple frontal and parietal foci in 2 cases); regional cortical-subcortical red softening in 10 cases (frontal in 1 case, parietal in 4 cases, and fronto-parietal in 5 cases); gross intracerebral hemorrhage in 1 case; gross central softening in 1 case; cortical-subcortical red softening combined with central red softening in 1 case, and chronic cortical softening associated with central cyst formation in 1 case (fig. 3).

In the 12 cases of thrombosis of the internal cerebral veins, the resultant lesions were distributed as follows: A limited number of small hemorrhages in corpus callosum in 1 case; gross hemorrhage in cerebral white matter in 1 case; hemorrhagic softening of the

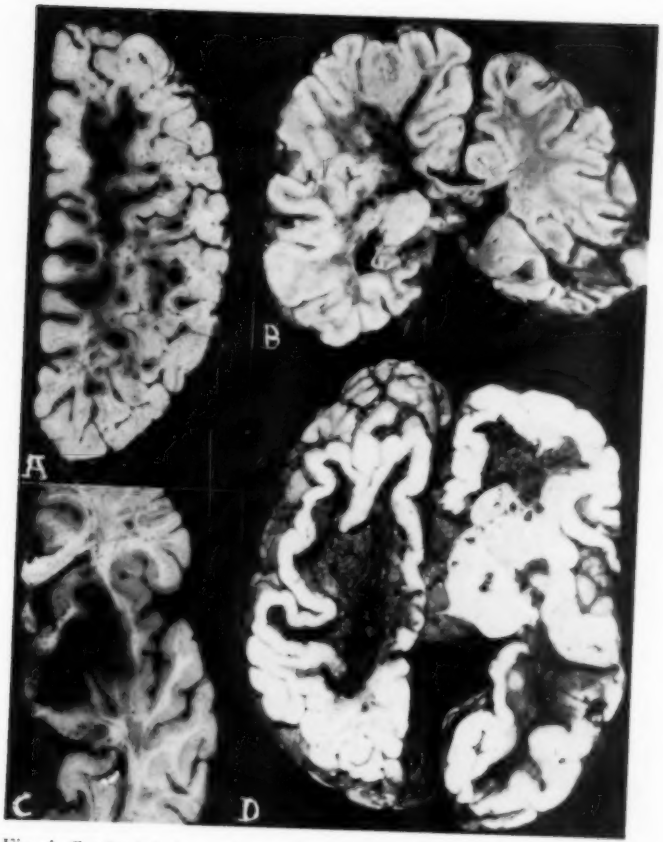

Fig. 4. Cerebral lesions after thrombosis of the internal cerebral veins. A. Multiple focal hemorrhages of cerebral centrum. B. Irregular focus of red softening of one hemisphere. C. Irregular distribution of focal hemorrhages in the basal ganglia. D. Extensive but irregular red softening of cerebral centrum. Right hemisphere has been horizontally sectioned at a lower level to show focal hemorrhages into the basal ganglia.

basal ganglia and adjacent white matter in 8 cases (thalamus and corpus striatum alone in 5 cases); and gross hemorrhage into the cerebral centrum associated with red softening in 2 cases (fig. 4).

In the group of 10 cases in which both the superior longitudinal sinus and the internal cerebral veins were thrombosed, the distribution of the individual lesions occurred as follows: external red softening alone in 1 case; external (cortical) associated with inter-

nal (white matter) red softening in 2 cases; red softening of the basal ganglia and regional white matter in 6 cases; and gross hemorrhage into cerebral centrum associated with red softening in 1 case.

Certain significant conclusions seem to present themselves after reviewing the cerebral lesions in this series of cases. These conclusions may be stated as follows:

1. Thrombosis usually begins in the superior longitudinal sinus with secondary extension into the superior cerebral veins. Exceptions do occur, however, and death may supervene from thrombosis of the superior cerebral veins before the longitudinal sinus is actually occluded.

2. The stages of development of the cerebral lesions consequent to thrombosis of the superior longitudinal sinus and its afferent veins appear to be as follows: (a) hyperemia, at first evident only microscopically, then becoming grossly apparent, (b) cortical and subcortical edema, (c) subarachnoid (not infrequently associated with subdural) hemorrhage, (d) cortical-subcortical softening marked by petechial hemorrhages, (e) independent softening and gross hemorrhage into the cerebral white matter.

3. The tendency for red softening to involve both the cortex and subcortex, the latter to an irregular degree seems to be an important characteristic of the external cerebral lesions.

4. The stages of change following thrombosis of the internal cerebral veins are not so well defined and there is a considerable variation in the distribution of the resultant lesions. The basic lesion is a red softening incident to retrograde distension and rupture of the small tributary veins. This is initiated by a few focal hemorrhages which became progressively increased in number leading to a confluence of these foci with breakdown of the intervening tissues.

5. Although following thrombosis of the internal cerebral veins, the basal ganglia are predisposed to be primarily and predominantly involved, in a goodly number of cases the regional white matter may be selectively affected by the process. The rule, however, is for both the basal ganglia and enveloping white matter to undergo red softening.

6. The borders of areas of red softening usually present a very irregular contour within the cerebral centrum.

7. The distribution of the lesions in the two cerebral hemispheres is usually not symmetrical; in fact, one side of the brain alone is not infrequently affected.

8. When both the superior longitudinal sinus and the internal cerebral veins are thrombosed, the resultant lesions seem to be largely secondary to thrombosis of the internal vessels.

9. In either case (external or internal venous thrombosis) there appears to be a predilection of localization of lesions to the parietal regions but the frontal lobes are by no means excepted.

10. The peculiar variant in both external and internal venous occlusions is the irregular and often widely scattering of foci of red softening. At times such isolated foci are quite sharply circumscribed.

An evaluation of the lesions resulting from thrombosis of the superior longitudinal sinus and/or the internal system of veins indicates that there is a wide divergence in the nature, degree and distribution of the cerebral lesions. It must therefore be concluded that if patients so affected could survive for any significant period of time, the late residuals should present a similar wide variation in their nature and distribution rather than present any stereotyped pattern.

IS IT POSSIBLE FOR AN INDIVIDUAL TO LONG SURVIVE A COMPLETE OCCLUSION OF THE INTRACRANIAL VENOUS CHANNELS?

The answer to this question must, with some qualifications, be answered in the affirmative. This is particularly true of the dorsolateral external venous system in which anastomatic veins make it possible to shunt venous blood around thrombotic obstructions in the larger dural sinuses. There is both clinical and experimental evidence to prove this point. As far as the lateral sinuses are concerned, there have been found complete organized occlusions of one of these channels presumably the result of a previous otitic infection although during life the patient presented no clinical manifestations of this obstruction. Moreover, in the past when otitic thrombosis of the lateral sinus was not so uncommon, the surgeon ligated the internal jugular vein with impunity, knowing full well that collateral channels could take care of the altered venous drainage. Although a somewhat different situation exists in case of the single superior longitudinal sinus, it is now recognized that the portion of this channel which lies anterior to the point of entrance

of the Rolandic veins can also be sacrificed with impunity (Jaeger, 1942).[27] Furthermore, in case of a slow occlusion of the more vulnerable posterio portion of the sinus, as by a meningeal tumor, no untoward symptoms arise even though this portion of the sinus is resected together with the new growth. In experimental animals, resection of this sinus fails to provoke any crippling residuals (Schlesinger 1939).[11]

One must therefore admit the theoretic possibility of survival from a thrombotic occlusion of the superior longitudinal sinus. This assumption is supported by actual case studies in which thrombosis of the sinus and its residual cerebral lesions were verified at autopsy. That this does not commonly occur, however, is evidenced by the fact that so very few cases have been reported. It is necessary to review briefly these examples to grasp the real significance of this fact.

Bailey and Hass (1937)[28] reported two examples of prolonged survival after thrombosis of the superior longitudinal sinus which seem to be unequivocal; a third which was uncertain as to its cause (their Case 1) will not be reviewed. In their Case 2, an infant developed a diarrhea associated with a febrile state *aet* 1 month. This was followed by a progressive downhill course until death 9 months later. At autopsy, an old organized thrombus was found in the middle third of the superior longitudinal sinus. A new formed membrane invested both cerebral hemispheres. The meninges were thickened, the parietal convolutions were somewhat atrophic but not softened although vascular proliferation with meningeal fibrosis was conspicuous microscopically.

In their third case, Bailey and Hass (1937) reported the history of an infant who died *aet* 3½ months. When one month old, the baby developed a diarrhea followed by convulsive seizures. It became generally spastic. At autopsy, a generalized atrophy of the cerebral hemisphere and shrinkage of the upper parietal and occipital convolutions was found to be associated with thickening and hemorrhagic staining of the arachnoid. The superior longitudinal sinus was occupied in its anterior half by an organized and canalized thrombus, which extended into the afferent veins. A laminar loss of nerve cells, focal softening, cyst formation and gliosis were evident in the cortex on microscopic examination. The cortical lesions tended to overflow into the underlying white matter. There also was a diffuse fibrosis of the leptomeninges.

More recently, Bailey[29] has studied three additional cases of temporary recovery from thrombosis of the superior longitudinal

sinus including a study of their residual lesions. Because these cases are to be published by Dr. Bailey, it will only be noted here that thrombosis of the superior longitudinal sinus occurred in each of three children coincident with a febrile state and died 11 months, 9 months and 20 months thereafter. The clinical course which was progressively downward, was characterized by hyperkinetic and paralytic phenomena, associated with mental deterioration. At autopsy, in addition to the organized and canalized thrombi in the superior sagittal sinus and afferent veins, degenerative changes were found in the cortex with extension into the underlying white matter and, to a degree, also in the basal ganglia. Microscopic study confirmed the irregular distribution of the cortical-subcortical lesions as well as fibrosis and hemosiderosis of the leptomeninges. The destructive character of the cortical lesions was conspicuous.

The present writer has had the opportunity to investigate still another case which is to be reported in some detail elsewhere (Courville, 1958)[30]. An infant of 19 months developed a diarrhea and vomiting leading to a state of dehydration. A generalized spasticity ensued. After a downhill course, death occurred 70 days after onset from pneumonitis. At autopsy, a marantic type of thrombosis of the superior longitudinal sinus was found to be associated with a neomembrane over the right cerebral hemisphere and a diffuse but irregular softening of the cerebral cortex of both parieto-occipital regions and of the basilar surface of the right temporal and occipital lobes. A huge blood clot was found in the right frontal lobe. The centrum of the upper parietal and occipital lobes and of both temporal lobes were occupied by irregular cystic cavitations (fig. 5.) Microscopically, the meninges were somewhat thickened, the cortex and subcortex were irregularly softened. Focal hemorrhages were still apparent in both the cortex and subcortical white matter.

Although these few cases must represent an imperfect picture of the total situation, their very scarcity suggests that survival of the superior longitudinal sinus after thrombosis must be very unusual. Moreover, it seems to be the rule that after such an occlusion the clinical course is progressively downward leading to a fatal issue. The length of the survival period is inversely proportional to the severity of the cerebral lesions. The implications are that any prolonged degree of survival of thrombosis would probably be accompanied by an irregular cortical-subcortical scarring associated with meningeal fibrosis with a more or less persistent pigmentation.

The clinical situation in case of thrombosis of the internal cerebral veins seems to be a much more serious one. A statement made over 20 years ago after a review of this problem (Ehlers and Courville, 1936),[17] seems still to be true, viz., that complete thrombosis of the internal cerebral vein is invariably fatal. At least no known case has been reported whose residual cerebral lesions would suggest that thrombosis of these veins had previously taken place. This is true of course, unless the argument that status marmoratus is a residual of this disorder can still be proven. The final discussion of this possibility will be considered in the following section.

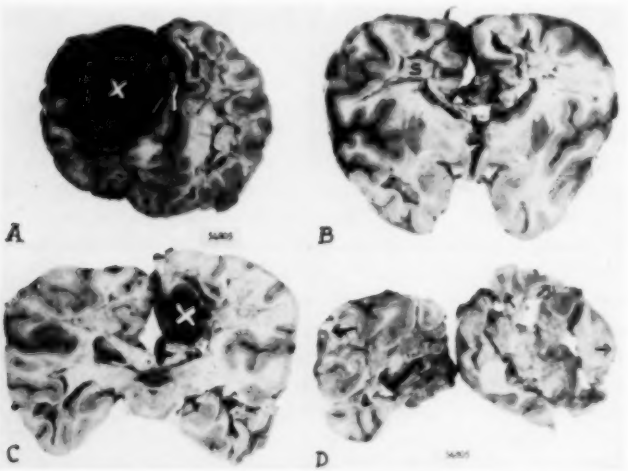

Fig. 5. Residual changes as found 70 days after thrombosis of the superior longitudinal sinus. A. Gross hemorrhage (x) still evident in right frontal lobe with irregular subtotal softening of centrum of left frontal lobe. B. Irregular subtotal softening of the upper centrum of both cerebral hemispheres at level of lenticular nuclei. Note isolated "sequestrum" (s) of white matter in right hemisphere. C. Irregular subtotal softening of upper centrum and white matter of both temporal lobes at level of pulvinar of thalamus associated with gross blood clot (x) in medial aspect of left paracentral lobule. D. Irregular subtotal softening of centrum of both hemispheres associated with cortical-subcortical softening (arrows) of the parietal lobes.

EVALUATION OF THE EVIDENCE

Having given consideration to the various acute and subacute lesions of the cerebral hemispheres consequent to thrombosis of the superior longitudinal sinus and/or the internal cerebral veins, it is now possible to evaluate this evidence in the light of the original

proposition. Can venous channel thrombosis be responsible for the development of nodular cortical atrophy, chronic cystic degeneration of the cerebral white matter, and status marmoratus.[2] Each of these lesions will be considered separately.

Nodular Cortical Atrophy ("Mantle Sclerosis") as a Possible Residual of Longitudinal Sinus Thrombosis.—When one considers the location of the areas of cortical change following thrombosis of this sinus and compares them to the location of the irregular lesions which characterize nodular cortical atrophy, the possibility of a causal relationship must be admitted. This is also true when the irregular type of cortical change in the two conditions is compared. It was therefore not unreasonable to consider this relationship when a case of an old thrombotic occlusion of the superior longitudinal sinus was found to be associated with a bilateral upper central and parietal localization of nodular cortical atrophy. At least three such instances have been reported in the literature and these cases must be carefully evaluated.

Norman (1936)[31] reported the case of a 5½ year old idiotic and spastic child with nodular cortical atrophy of both upper central and parietal lobes. The lumen of the superior longitudinal sinus was partially obliterated in this region. The cause of this occlusion was uncertain, possibly being the result of a septic thrombosis during pregnancy. However, the child had been seriously asphyxiated at birth. It is therefore doubtful whether thrombosis was acutely incident to the mechanics of labor and whether it was actually the cause of the cortical atrophy. Neonatal asphyxia must certainly be considered as an alternate hypothesis.

Hallervorden (1939)[31] described a similar case in an idiotic 2 year old boy who had been born prematurely. He developed tetraplegia dating back to birth. At autopsy softening of the upper part of both cerebral hemispheres superimposed on a chronic hemiatrophy was found. The cause of the softening was considered to be a recent thrombosis of the superior longitudinal sinus which had been engrafted upon an older occlusion of this channel. The weakness in this case lies in the uncertainty of the "old" thrombosis of the sinus and its relation to mechanics of difficult labor even if this had actually taken place. Although the details of pathological change were not clear enough to prove a true residual of sinus thrombosis, the lack of a definite recent ictus for the thrombosis and a clear downhill clinical course make it impossible to consider this case a clear cut one.

More recently Dekaban and Norman (1958)[33] described the

case of a 28-year-old man who had an acute illness of some sort *aet* 2½ years. Nothing significant about the patient's birth was noted, although he had convulsive seizures immediately following delivery and at the age of one year. He had subsequently developed a hemiplegia. At autopsy sclerotic atrophy of the dorsolateral and medial convolutions of anterior left frontal cortex and the medial aspect of the occipital cortex was found. Subcortical cyst formation and regional demyelination was also present. A partial old occlusion of the anterior part of the superior longitudinal sinus was considered as the most likely cause of the cerebral changes. The occurrence of convulsions prior to the episode presumed to be the development of thrombosis, the occurrence of occlusion of the sinus only in the frontal region, and the absence of occlusion posteriorly where sclerotic cortical changes had taken place, raises considerable doubt as to the actual mechanism of the cerebral changes in this instance.

A number of arguments against the overall conclusion that an occlusion of this sinus is the invariable cause of this type of cortical atrophy, may be listed as follows: The common symmetrical, and at times multiple symmetrical localization of areas of cortical atrophy in the dorsolateral frontal, and middle central and occipital cortex, the frequent association of this type of atrophy with porencephalic defects, the limitation of this chronic change to the cortex in contrast to the areas of irregular softening following venous thrombosis which frequently "overflow" into the subcortical white matter, the absence of pigmentation and meningeal fibrosis in nodular cortical atrophy and finally the absence of isolated foci of softening in the underlying cerebral white matter (fig. 6). Not only do the characteristic findings in nodular cortical atrophy tend to argue against their venous origin; these changes are definitely suggestive of their genesis in an arterial ischemia (Courville, 1959).[34] It must be concluded, therefore, that the weight of evidence now available seems to be against the origin of nodular cortical atrophy in thrombosis of the superior longitudinal sinus.

Chronic Infantile Cystic Degeneration of the Cerebral Centrum as a Possible Residual of Venous Channel Thrombosis.—The formation of cystic cavities in the cerebral white matter as a result of thrombosis of either the superior longitudinal sinus or the internal cerebral veins is a demonstrated fact (fig. 7). As a rule these irregular cavitations are more or less isolated especially those following thrombosis of the superior longitudinal sinus. Further-

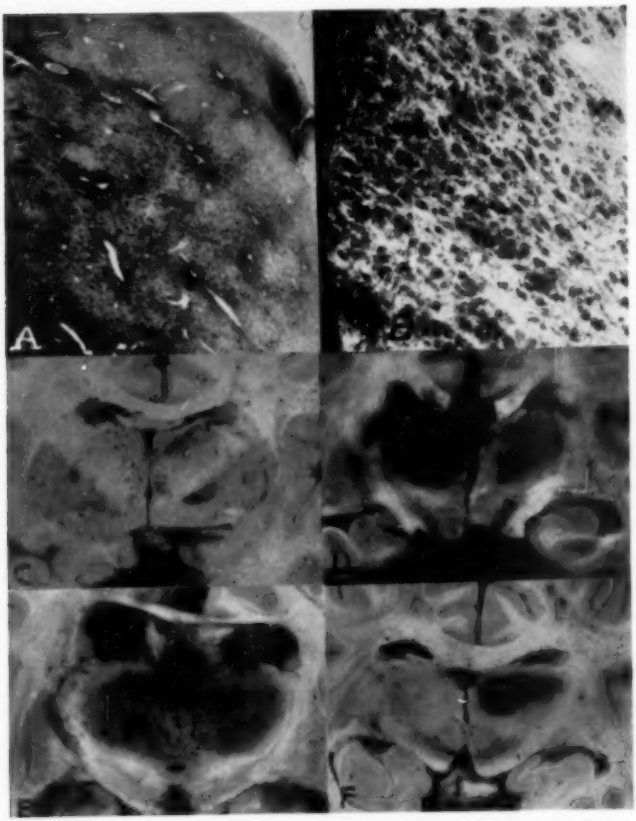

Fig. 6. Nodular cortical atrophy compared with cortical alterations consequent to thrombosis of the superior longitudinal sinus. A and B. Typical change in nodular cortical atrophy. Sharp delineation between the altered cortex and underlying white matter is evident. C. Invasion of underlying white matter even in focal lesions after longitudinal sinus thrombosis is clearly evident. D. Involvement of subcortex even in minor lesions (a) and extensive involvement of white matter in gross lesions (b) is quite evident. E. Gross destruction of cortex and subcortex in larger hemorrhagic lesion is quite clear. F. Irregular cortical-subcortical softening (arrows) is evident in case with survival for 70 days of thrombosis of longitudinal sinus.

more, the practically invariable irregular and often serious involvement of the cerebral cortex after thrombosis should distinguish this effect from an architecturally intact cortex which is almost the rule in chronic cystic degeneration. In case of thrombosis of the internal cerebral veins, however, much of the interior portion

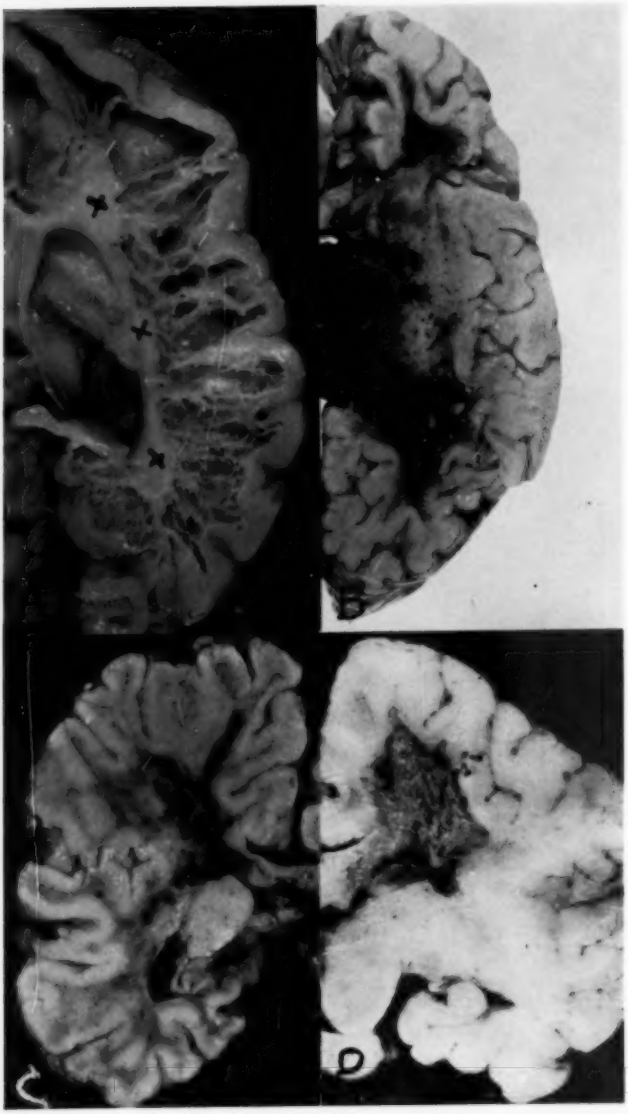

Fig. 7

of the brain, particularly that enveloping the basal ganglia, may be hollowed out. This very extensive spread of cavitation with its seemingly invariably fatal outcome rules against survival of an infant for more than a few days after internal venous occlusion has taken place. Moreover, the inclusion of the basal ganglia in this gross defect further mitigates against any prolonged survival. And yet it would be necessary to have an extensive thrombosis of both the superior longitudinal sinus and the internal system of veins to achieve even approximate total replacement of the cerebral white matter by cystic cavities.

One is obligated to conclude therefore that the distribution and extent of the lesions in the chronic cystic degeneration (practical total cystic replacement of the white matter with architectural preservation of the cortex and basal ganglia) cannot be compared with the hemorrhagic necrosis of the interior of the cerebral hemispheres following thrombosis of the internal venous system. The likelihood of chronic cystic degeneration being a result of venous channel thrombosis is therefore quite remote.

STATUS MARMORATUS AND THROMBOSIS OF THE INTERNAL CEREBRAL VEINS

There remains the question whether status marmoratus, which is characterized pathologically by the presence in excessive number of myelinated fibers in the basal gray masses, less often in the cortex as well, can have its origin in an occlusion (or phlebostasis) of blood in the internal system of cerebral veins. That such venous stasis or actual thrombosis may occur in the early postnatal period, is certainly possible. That it is a result of dystocia and consequent to excessive moulding of the head, on the other hand, is very doubtful, as indicated by case reports already cited. It is also to be seriously questioned whether a newborn infant could survive occlusion of these veins for any significant length of time. A comparison of the distribution of hemorrhages in the basal ganglia and the common location of the bundles of myelinated nerve fibers in status marmoratus is also significant (fig. 8). The hemorrhages are

Fig. 7. Central cystic lesions of chronic cystic degeneration compared with central changes in venous channel thrombosis. A. Typical case of central cystic degeneration of infancy showing sharp delineation between central cysts and grossly normal cortex. Sparing of focal masses of paraventricular white matter is to be noted (x). B. Subtotal destruction of centrum by red softening incident to venous thrombosis with sparing of subcortical white matter but with severe damage to the basal ganglia. C. Irregular focus of paraventricular red softening with sparing of subcortical white matter. D. Destruction of central white matter and adjacent corpus callosum with sparing of subcortical white matter in case of internal venous thrombosis.

usually irregularly distributed and at times unilateral while in status marmoratus, the bundles of myelinated nerve fibers are usually symmetrical as well as bilateral, except in association with severe one-sided cerebral cortical atrophy, and more condensed in the outer aspects of the caudate nucleus, the upper portion of the putamen, and in the dorsomedian nucleus of the thalamus. The

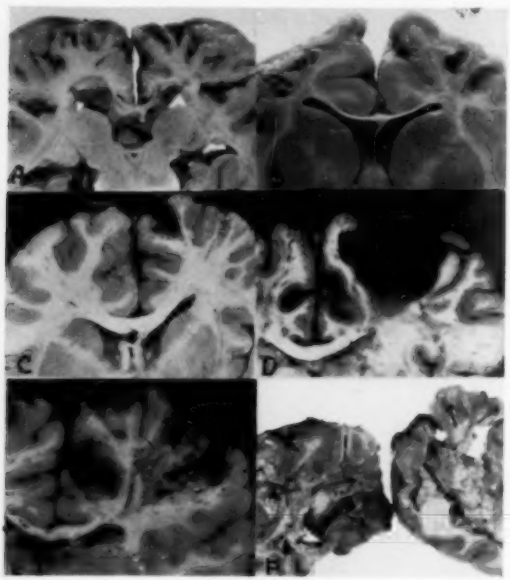

Fig. 8. The characteristic lesion of status marmoratus compared with alteration in basal ganglia after occlusion of internal cerebral veins. A. and B. Typical appearance and pattern of distribution of bundles of myelinated nerve fibers in lateral aspects of thalamus. C. Showing sites of predilection for focal hemorrhages in early lesion. Note localization in upper and medial thalamus, tail of caudate nuclei and globus pallidus as well asymmetry of lesion. D. More severe lesion showing irregular and patchy arrangement of focal hemorrhages as well as "overflow" into internal capsules. E. Gross lesion with necrosis of central part of both thalamic masses with "overflow" into internal capsule on right. E. Isolated lesion in the left thalamus showing tendency to involve upper portion of this mass.

fact that alterations in the basal ganglia incident to occlusion of the veins of Galen are usually not limited to the gray mass but also involve the regional white matter, and the fact that these lesions are focal hemorrhages which would ordinarily be followed by focal cavitations should exclude status marmoratus as a residual effect. In this last named disorder no associated focal lesions, posthem-

orrhagic or otherwise, are to be found in the regional white matter. By what strange biological alchemy can a rounded *defect* left after absorption of a perivenous hemorrhage be transformed into a *bundle* of myelinated fibers invading the basal ganglia from the enveloping white matter?

SUMMARY AND CONCLUSIONS

Since the time of Gowers, some have suspected that the patches of nodular atrophy of the cerebral cortex, dating back to some event in early life, were the result of thrombosis of the superior longitudinal sinus. As time has gone by, this same mechanism (together with thrombosis of the internal venous system) has been evoked to account for chronic cystic degeneration of the cerebral white matter and status marmoratus of the basal ganglia. As a result of the writer's personal investigations into the pathogenesis of these lesions as well as his acquaintance with the characteristic cerebral residuals of venous thrombosis, it has become increasingly apparent to him that there were a number of serious flaws in this concept. As a basis for this investigation of the theory, the literature dealing with the pathology of intracranial venous thrombosis, especially that occurring in early life was reviewed. The cases of this disorder verified at autopsy (53 in number) which have come under the writer's personal scrutiny were also scrutinized.

On the basis of this investigation, the following conclusions have been reached: (1) Thrombosis of the intracranial venous channel is of rare occurrence in the newborn. (2) When this does occur, it is usually found in a premature infant afflicted with debility rather than a result of cranial distortion incident to dystocia. (3) The lesions secondary to thrombosis of the superior longitudinal sinus are subdural and subarachnoid hemorrhage, red softening of the cortex and subcortex, and isolated foci of subcortical red softening. (4) The secondary lesions of thrombosis of the internal cerebral veins are red softening leading to irregular defects or diffuse necrosis of the basal ganglia and the deeper portions of the cerebral white matter, as well as occasional gross hemorrhage into these areas. (5) The chief argument against the concept that thrombosis of the superior longitudinal sinus is the cause of nodular cortical atrophy is not only the difference in the pattern of distribution of these lesions but also the fact that the cortical changes resulting from thrombosis overflow irregularly into the underlying white matter. (6) Although red softening of white matter incident to venous thrombosis can produce focal cavitations

in this location, such cavitations have a dissimilar and irregular distribution, tending to spare the subcortical white matter, and seem to be invariably fatal within a few days. (7) The absence of associated significant lesions in the white matter, the irregular distribution of petechial hemorrhages in the basal ganglia as compared to the common locations of the abnormal bundles of white fibers, as well as the nature of the lesions themselves controverts the concept that status marmoratus has its genesis in thrombosis of the internal cerebral veins.

It may therefore be stated with reasonable certainty that although a paralytic state (progressive decerebration with spasticity) may follow thrombosis of the superior longitudinal sinus in early life, the clinical course is progressively downward to a fatal issue, usually within a year. This course is also marked by progressive failure of mentation. Based upon the few reported cases, the nature and distribution of the lesions found at autopsy do not correspond either grossly or microscopically with those of nodular cortical atrophy or other lesion-complexes found in cases of cerebral palsy.

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Letter to the Publisher . . .

Rio de Janeiro, Brasil
March 18, 1959

As a long-time friend of my father, Dr. A. Lopes Cançado, I thought, Mr. Gaylor, that you would be interested in knowing of my memorable meeting with Dr. Jonas Salk, during my recent visit to New York.

As a medical student myself, you can imagine the great honor I felt when I was selected to represent the people of Brasil as their emissary to carry a message of heartfelt gratitude to this eminent personality!

The choice which so happily fell on me, came as the result of a campaign toward the final months of 1958, when one of Brasil's leading newspapers, *O Globo*, carried on a campaign for the purpose of picking out a young Brasilian who had been a victim of poliomyelitis and had successfully conquered it—not alone physically, but spiritually.

The "message" I took was in the form of a silver and gold album, the cover of which presented six silver calling-cards, each with written greetings for Dr. Salk from the Minister of Education and Health, the Minister of Justice, the Mayor of Rio, and other of my country's "first citizens."

It is almost impossible to describe my deep impression of this extraordinary doctor, and to emphasize his greatness, let me tell you that the interview, scheduled (at the Waldorf-Astoria) to last just ten minutes, went on for one hour! As is true of all geniuses, Dr. Salk has charming simplicity, and one characteristic that has lingered with me, is his deep, penetrating eyes—they make him look like a superman! He asked me many questions about my country, its people and, of course, about vaccination programs in Brasil. I told him that everywhere, our doctors are doing all possible not to miss vaccinating a single child, and that *O Globo* had helped tremendously in the good work.

I have a conviction that everywhere, people—particularly parents and doctors who care for children—pray that humanity may be sent more men like Dr. Salk, because our modern world, with its terrible struggles, its lack of mutual understanding, its terrifying problems and menaces, desperately needs them.

I feel that only men of the selfless stature of Dr. Salk can alleviate the pains of suffering humanity and lead her to lasting peace and happiness!

Wanda L. Magon Lopes Cançado

A CASE OF FALLOT'S TETRALOGY WITH AN ATRIO-SEPTAL DEFECT COMPLICATED BY A LUNG ABSCESS

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A Sinhalese girl, 5 years old, was admitted to the Children's Hospital, Colombo on 1-7-58 with a history of fever, cough and breathlessness of 10 days' duration.

She was the eldest girl in the family and was born at term, delivery being normal. The parents noticed that the child was breathless from birth; in addition to the mild breathlessness she used to get attacks of acute dyspnoea from the third month onwards. During each attack her lips and finger tips used to become blue in colour, each such attack was preceded and accompanied by fever and cyanosis.

At no stage of the illness did the child have any swelling of the feet or abdominal enlargement. Throughout her life she was always breathless and could never play nor run about with other children. Any form of exertion made her acutely dyspnoeic and cyanotic. About 12 days prior to admission to the hospital, the child developed fever and her breathlessness increased. Two days later she developed a cough which was not paroxysmal nor in the early stages was it productive. In the last few days of her illness there was a little purulent expectoration.

The child was treated at two local hospitals and then referred to the Children's Hospital, Colombo. On admission her temperature was 99.8° F.

On examination the child was found to be dyspnoeic and the alae nasi were working, the veins of the neck were engorged; there were no visible pulsations in the neck but cyanosis was present on the tongue, lips and fingers; the fingers and the toes were also clubbed. The liver was palpable three fingerbreadths below the costal margin but there was no oedema in any part of the body nor in the extremities.

The apex beat was palpable in the 6th left intercostal space in the anterior axillary line and was tapping in character. A parasternal heave was also palpable. There was a systolic thrill in the pulmonary area. The pulmonary 2nd sound was not palpable but single and faint. On auscultation a rough systolic murmur was heard in the pulmonary area as well as in the apical area.

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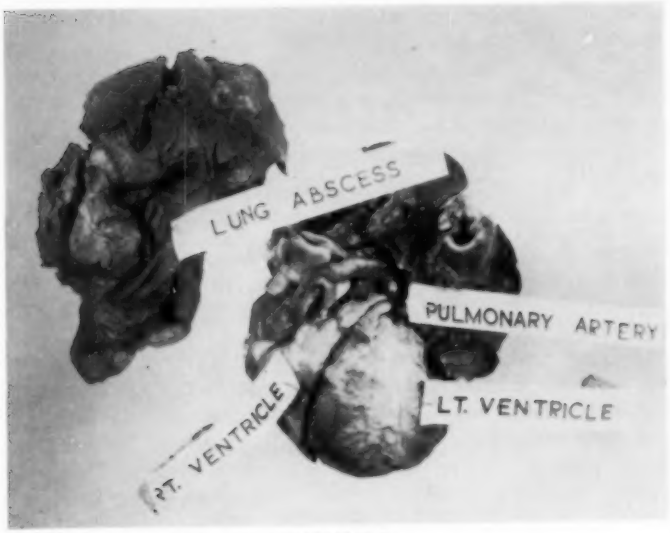

FIGURE 1

The blood pressure was: Systolic 90 mm Hg; Diastolic 50 mm Hg and the pulse rate was 102 per minute.

Examination of the respiratory system revealed that the trachea was in the midline. Vocal fremitus and resonance were equal on both sides and the percussion note was resonant in all areas. There were a few coarse crepitations at both bases.

The child was given a course of crystalline penicillin and sulphamethazine. The day after her admission the temperature fell to 98.4° F. At this stage her breathlessness recurred, the pulse rate rose to 160 per minute. Her condition continued to deteriorate steadily and she died 11 days after admission. At this stage the child was getting intravenous and oral Digoxin and intramuscular Streptomycin in addition to the penicillin and sulphamethazine.

LABORATORY DATA

Hb	11.5% (Cyanhaematin)	P.C.V.	37%
R.B.C.	3,550,000 per cmm	M.C.V.	105/cu. microns
W.B.C.	10,400 per cmm	M.C.H.	33 mic. mic. gr.
		M.C.H.C.	31 Gm. %

Polymorphs 45%
Lymphocytes 49%
Eosinophils 6%

Blood picture: Slight anisocytosis. *Mantoux reaction*: Negative.
Fluoroscopy: The lung fields were oligaemic; no hilar dance nor

any abnormal pulsations were seen. Dextro-position of the aorta was visible.

X-Rays: The heart was slightly enlarged and has a coeur-en sabot appearance together with a shadow suggestive of a pleural effusion at the right base. The lung fields were oligaemic. There was also a circular shadow within the heart shadow in the right lateral projection.

E.C.G. Rate — 150 per minute
Rhythm — regular
Axis deviation — right
Position — vertical
Rotation — Anticlockwise
Slight enlargement of both ventricles.

A clinical diagnosis of Fallot's tetralogy was made which was confirmed by X-rays and screening.

Autopsy revealed the following: Lungs: The right lower lobe was dark red and adherent to the chest wall. In this lobe there was an abscess which was one-half inch in diameter. Heart: Both left and right ventricles were hypertrophied. There was an overiding aorta with a slightly stenosed pulmonary artery. The pulmonary valve was tricuspid. There was an atrioseptal defect as well as a high ventricular septal defect. No pulmonary embolus were seen.

DISCUSSION

The child had cyanosis from early infancy, clubbing of the fingers and toes, a systolic thrill and murmur in the 2nd left intercostal space, a systolic murmur at the lower end of the sternum, a faint pulmonary second sound and signs of right ventricular enlargement. The obvious diagnosis was Fallot's tetralogy. This was confirmed radiologically by the coeur-en-sabot shaped heart, oligaemic lung fields and right sided aorta.

The post-mortem however showed that this was not a true case of Fallot's tetralogy because in addition to these ventricular defects there was an auricular septal defect as well.

The interesting feature in this case was the lung abscess which is a rare complication of Fallot's tetralogy. Cerebral abscess due to paradoxical embolism may occur in about 5% of cases.

A review of Taussig's[1] Congenital Malformations of the Heart does not reveal a single similar case; but Keith, Rowe and Vlad (1958)[2] state that an atrial septal defect was found in 33% of 60 autopsies in Fallot's tetralogy.

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HEADACHES IN CHILDREN **

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Pediatricians, by the very nature of their specialty, deal with all types of problems affecting the health of children. The pediatric specialty has usually been in the forefront in prevention of disease and disability. Despite this, pediatricians have paid little attention to headaches in children, a frequent complaint in chronic pathologic conditions in childhood.

Recently, there has been a keener appreciation of this symptom, partly through recognition of the relationship of general systemic factors upon the local complaint. Headache is a symptom which may occur in almost any organic or psychogenic disturbance. The present analysis will be limited to a consideration of some general principles.

METHOD OF PROCEDURE

We proceeded to investigate by utilizing the facilities of our out-patient clinic and also screened the charts of our private patients for this complaint. Following this we recalled these patients to the clinic or office for consultation. When they appeared in the clinic or the office we inquired as to the localization and the time of occurrence of the headache. This was followed by laboratory examinations, x-rays of the skull, and electroencephalogram or psychiatrist, where indicated. Our major consideration was to treat each patient as a unit. A careful history as to diet, school, work, play and environment was investigated. At the conclusion of this survey we attempted to evaluate the findings and then prescribe the appropriate treatment.

The following lists a total of 37 cases completely worked up and from which we tabulated our results.

CASE HISTORIES, CHART 1

The majority of cases (32) were in the seven to sixteen years of age group, and 5 cases in the three to five years age group. From the histories we traced the headaches in 45% of our patients

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CHART I CASE HISTORIES — HEADACHES IN CHILDREN

Case No.	Age	Sex	Region of Headache	Duration	Symptoms	Diagnosis	Remarks
44501	10	M	Top & right side of head	12 months	Headache, fullness after meals	Migraine, possible allergy	
44502	13	F	All over	10 years	Headache, petitmal	Epilepsy—positive diagnosis from E.E.G.	
44503	12	F	Occipital	3 years	Headaches after emotional stress	Tension	Emotional upsets started headache
44504	8	F	Frontal	11 months	Stomach pains, headaches	Food allergy, possible migraine	
44505	4½	F	All over	14 months	Headaches, crying spells	Tension headaches, psychogenic	Parents advised to discuss their problems not in presence of child
44506	6	M	Frontal, over eyes to left side	11 months	Headaches daily before going to school —tired	Tension, emotional	Child given hematinic for low hemoglobin (74%)
44507	9½	M	Temporal	3-4 years	Headaches, overweight	Migraine, obesity	Wigraine® reduced to ¼ tablet and rash subsided
44508	5½	M	Top head	5 months	Headaches after exhaustive play	Tension	
44509	9	M	Frontal	12 weeks constant	Had high fever, 106° and headaches	Virus pneumonia with cerebral involvement	
44510	16	F	Back of head	3 months	Headaches, poor sleeper, restless	Overworked, menstrual irregularity—tension headaches	After school this child worked in mother's office
44511	8	M	Frontal	10 months	Headaches when overheated—in school environment closed atmosphere	Psychogenic—has claustrophobia	
44512	8	M	Left side of head	1 year	Child complains of headaches during school hours	Maladjustment	Addition of tranquilizer helped
44513	6	F	Frontal	3½ weeks	Every morning child gets headaches before going to school	Post Encephalitis	Child to remain at home remainder of term
44514	7	M	Frontal—over eyes	5 months	Bedwetting & headaches	Enuresis, emotional	Referred to neurological service
44515	5½	M	All over	6 months	Headaches, occasional nervousness	Post-injury headaches, possible subdural hemorrhage	
44516	6½	M	Frontal	6-8 months	Headaches, vomits	Migraine—possible allergy	
44517	14	F	Left side near nose	2 years	Headaches, with head colds	Allergic—migraine	Child has an allergy
44518	13	M	Frontal, right side	1 year	Headaches precede & follow epileptic attacks	Petit mal-positive E.E.G.	E.E.G. still abnormal—paroxysmal cerebral dysrhythmia—continue medication

44519	9	F	Left side, occasionally right side, too	3 years	Headaches following injury	Post-concussion syndrome of headaches —x-ray skull, negative	No headaches while on medication—she spent two weeks in hospital
44520	10	F	Frontal & temporal	1 year	Headaches following auto accident—fever	Possible injury to hypothalamus	Because of fever—damage to hypothalamic area possible
44521	6	F	All over head	4 months	Headaches before going to school	Psychogenic	
44522	5½	F	Right side of head	1 month	Headache after meals—pains in stomach	Allergic	
44523	6½	F	Frontal and over eyes, occipital	2 years	Constipated, headache before bowel movement	Tension	
44524	9	M	Top of head, over eyes	6-8 months	Eyes painful, headaches watching TV	Migraine	
44525	8	F	Pounding, top of head	2-3 years	Tires easily, headaches	Obesity, migraine	Diet
44526	6	F	Frontal and back head	2 years	Headaches	Undetermined, possible migraine	
44527	5	M	Frontal & top of head	1 year	Headaches after Television, vomits, falls asleep & awakens with headache	Tension	
44475	7	F	Unilateral (right)	Intermittent (3-5 months)	Coryza, cough, headaches right side	Acute respiratory infection, asthmatic bronchitis—migraine	Headaches unrelieved — histamine effective for asthmatic involvement
44476	7	M	Occipital, throbbing in nature	1 year	Difficulty in breathing, sore throat & headaches	Enlarged tonsils & adenoids—migraine	Headaches persisted—advised A & T operation
44477	5	M	Right temporal	3 weeks	Headaches, nosebleeds	Deviated septum—migraine	Headaches continued—nose drops helped some
44478	12	M	Occipital—throbbing	Intermittent 1 year	Pains in head, upset stomach, constipation	Intestinal stasis—toxemia-migraine	Headaches persisted—routine established to control constipation and nausea
44482	14	F	Left temporal	2 years, occ.	Loss of appetite, eczema of skin, face —headaches, nausea	Anemia-wheat allergy-emotional—tension headaches	Headaches persisted—nutrition improved
44489	7	M	Patient unable to tell where headache is more severe	Intermittent 6 months	Headaches, fever; pains in legs & abdomen	Acute rheumatic fever-anemia-migraine	Headaches continue occasionally—joint involvements pain in abdomen improved
44490	3	F	Head hurts	Occasional 2 weeks	Headaches, restlessness, stomach aches	Allergy (Chocolate)	Headaches continue occasionally—allergic manifestations are improving
44491	13	M	Occipital—throbbing in nature	Occasional 3-4 years	Pain in head—visual disturbance—nausea	Head injury at 8½ years—sub-dural Hemorrhage	No improvement noted—child referred neuro-surgery
44493	4	F	Right temporal	8 months	Pain in right temporal region, occasional vomiting, urticaria	Migraine headache, probably due to allergy	Very little relief from headaches—urticaria improved
44494	10	M	Occipital, throbbing in nature	Intermittent 2-3 years	Chronic asthmatic attacks—headaches	Allergic-tension headaches	Headaches continue—occasional relief asthmatic attacks during cool weather

to the parents. It is generally believed that girls are more prone to headaches than boys; in fact, numerous investigators have so stated. However, in our series there are more boys than girls—22 boys to 15 girls. We may conclude then that there is no sex difference in those who suffer from this ailment in childhood.

From our findings we came to the conclusion that the most frequent type of headache encountered in our study was *migraine*. This form of headache is characterized by being unilateral, usually associated with gastrointestinal or ocular symptoms, usually preceded by psychologic or visual disturbance, and frequently followed by sleep. Heredity plays a great part in this type. The mechanism of migraine is doubtless vascular in origin; as pointed out by others, the constriction of the cerebral arteries produces visual and possibly other pre-headache phenomena prior to onset of the head pains. This is then followed by dilatation and distension of the cranial arteries in the region of the external carotid artery. It is this dilatation and increased pulsation that causes the headache. We classified 11 cases in this group.

The next most frequent type is the *tension* headache. These are characterized by having no prodomata or warning, usually bilateral, either frontal or occipital. They may be accompanied by nausea, vomiting, or anxiety. They may be periodic emotional upsets, conscious, unconscious, or stress. This type also produces changes in the cranial blood vessels together with spasm of the head, neck, and skeletal muscles, and may give rise to ocular and sinus involvement. These attacks may last for days or weeks. Many physicians have been under the impression that the most common cause of recurrent headache in children was errors of refraction. From our study, after routine ophthalmic examinations, errors in refraction played a minor role. There were eight cases in this series.

Allergic manifestations, food allergy particularly, have been found to play an important role in the headache complaints. Even psychic stimuli where certain foods are offered or observed by the patient, may bring on an attack of headache. The most frequent food offenders in this group are wheat, milk, oils, fish, eggs, and chocolate. Six of our cases were in this group.

Psychogenic factors may be associated with tension headaches. The cause of onset may be due to conflicts in the home or in the school. In other instances we have also noticed that when a mother constantly complains of headaches in the presence of her children or child, it inevitably prompts the child to follow the mother's

pattern. This may be an excuse for the child to avoid punishment or gain an advantage by complaining of a headache. These young patients frequently demonstrate hostility, aggressiveness, or resentment against their brothers, sisters, or even their parents. Many of them display evidence of a guilty feeling, which is frequently followed by headache.

The emotional or environmental aspects should not be overlooked in tracing the onset of headaches in children. It has been shown in adult studies that psychological conflicts may produce a variety of symptoms such as headaches, ulcers, and hypertension. In the child the early manifestation may be headache alone. From our studies it seems that emotional conflicts may produce an end-organ discharge either in the muscles or nerves, with resulting changes in the blood vessels of the head and neck. These changes cause the contractions in the muscles and dilatation of the blood vessels, thereby causing the head pains and headaches. All these changes do occur early in life and set a future pattern for emotional stress. Our analysis showed eight cases belonging in this group.

The following is a classification of the cases listed in Chart I:

TABLE I

Types of Headaches

Allergic	6
Migraine	11
Tension	8
Epilepsy	2
Psychogenic	8
Other	2
Total	37

We have frequently been asked how a doctor could diagnose headache in infancy and early childhood. From our observations we noted that rubbing of the head, crying, wrinkling of the forehead, or restlessness, may be an early sign of headache. Of course, observing the pattern of behavior in infancy during an attack and correlating that with a description of the area of involvement when the child can talk, gives us the clue. One observer who treated a child for migraine stated that he had evidence that the child apparently started his attacks at two weeks of age, the earliest on record.

In 1949, Vahlquist and Haskell[1,2] in a study of 31 cases in which the disease first appeared between one and four years of age, noted in one case a boy whose mother had menstrual migraine, the

infant's first attack occurred at the age of one year, when he suddenly turned pale and had an attack of vomiting. During the next two years, he had several attacks a week, always of the same type. When the child was three years of age he began to complain of pain in his head during the attacks.

In our own series, a boy of three years, his first attack started at two years of age. He had pains on the left side of the head, associated with nausea and vomiting. The attacks occurred when he was overtired from play or exposed to cold weather. In the latter case the father had been suffering from migraine for 15 years.

It is generally agreed the symptoms in children and adults are about the same, with these differences. In children the warning symptoms are loss of appetite, abdominal discomfort, tiredness, instead of hunger and irritability as in adults. The headaches in children at first may be minor and attention to the abdominal distress greater, but the headache increases in severity and gradually the abdominal symptoms subside, perhaps with vomiting. The symptoms in children are usually of shorter duration and the nausea more intense than in adults.

The psychogenic element in children seems to be of major importance, the children are usually nervous, show various behavior disturbances such as nail biting, and are of uneven disposition. The attacks are usually brought on by overindulgence in T.V. showings, little sleep, fatigue, and irregular meals.

From our study, the causes of headache may be due to any of the following conditions, each of which must be ruled out for a final diagnosis:

(a) Dilatation and distension of extracranial arteries.
(b) Involvement of sinuses.
(c) Inflammation of blood vessels.
(d) Involvement of nerves.
(e) Imbalance of sympathetic-parasympathetic nervous system
(f) Allergy.
(g) Emotional upsets.
(h) Tiredness.
(i) Trauma.
(j) Tumors.

Other factors causing headaches aside from those outlined in our findings, may be the result of nasal congestion which obstructs the sinuses, rare errors in refraction, inhalants, and food allergies. In the six cases with definite food allergies, chocolate was the most

frequent offender. This factor can be quickly ruled out by food elimination or testing; the former is more preferable.

Of the other cases listed in our series one child of eight and one-half years complained of headaches of three years duration. This was referred for brain surgery with subsequent good results. The other cases were epilepsy (petit mal) with frequent morning headaches.

TREATMENT

Regardless of the type of headaches, consideration must be given to the physical condition of the child. Investigation of the underlying condition for his or her discomfort should follow and this condition corrected, if possible.

(a) Allergy—which is indicated either by testing or elimination.
(b) Anemia, if any.
(c) Diet.
(d) Environment.
(e) Infection.
(f) Psychosomatic factors.
(g) Tension.

Concerning the treatment of headache, the physician has four main methods from which to choose: drug therapy, psychotherapy, physiotherapy, or surgery . . . as in brain tumor. The therapist may attempt either to give the patient symptomatic relief or to prevent the occurrence of headache entirely. The latter is obviously preferable, but most of our general treatment falls short of this ideal.

DRUG THERAPY

To relieve the headache, the physician must attempt the following: (1) raise the pain threshold. (2) to interrupt the mechanism producing pain. (3) to reduce the emotional tension and anxiety associated with the pain.

The effectiveness of the medication depends upon the physician who is prescribing same and the frequency of his consultation with the patient. It has been observed that patients improve if they are seen at frequent intervals. As one observer noted,[3] "The treatment of headache may be compared to that of diabetes. If one needs 100 units of insulin and only receives 80 units, the results are therapeutically inadequate."

Over the years many medications have been tested by medical practitioners. They now have a few on which they depend for

quick relief. These medications which raise the threshold of pain—the analgesics—only two groups are significant here: (1) The pain reliever (analgesic), phenacetin and aspirin, both plain and buffered. (2) Codeine.

The analgesic action may be secured by relatively small doses, such as 5-10 grains of aspirin or phenacetin. Larger doses fail to further raise the pain threshold. Codeine is the most effective of the analgesic drugs and in small doses (¼ to ½ grain) will raise the pain threshold higher than the antipyretic analgesics. In larger doses restlessness and nausea may be produced. The routine or indiscriminate use of codeine or other narcotics is not recommended. Since many vascular headaches are due to the dilatation and distension of the relaxed cranial arteries, their constriction is the most effective method of treatment.

Extremely effective is the method of treating migraine or tension headache by interrupting the pain producing mechanism. The vascular headaches are due to the dilatation and distension of the relaxed cranial arteries; therefore, it is of utmost importance to effect a constriction of the blood vessels. Here, ergotamine tartrate, an alkaloid of ergot, will produce vasoconstriction of the arteries, thereby reducing the pulsation in the cranial blood vessels. Many physicians have found a medication* containing ergotamine tartrate (vasoconstrictor) in combination with caffeine, acetophenetidin, and belladonna is very effective in the treatment of migraine and other types of headaches as indicated in the analysis (Table II) presented here.

Final results in 37 cases:

TABLE II

	Good	Fair	None
Allergic	9		
Migraine	8	2	1
Tension	7	1	
Epilepsy	2		
Psychogenic	2	2	
Other Illnesses	3		
Total	31 (83.8%)	5 (13.5%)	1 (2.7%)

Recently the tranquilizing agents—compounds derived from phenothiazine—have been recommended particularly for stress or tension headache. These have proven to be extremely helpful in conjunction with analgesics (aspirin and phenacetin). The phenobarbitals (barbituates) are not recommended because of the after effects these medications have on the patient.

*Wigraine ®

For over a century caffeine has been incorporated with aspirin or phenacetin for relief of headaches, particularly in adults. Some are advised to drink coffee to relieve their headaches. This has been helpful; small doses of caffeine usually suffice.

In other spheres of therapy, of course, we should have consultation with a psychologist or child guidance advisor.

There is a variance of opinion on the use of nicotinic acid. This medication given intravenously may give quick relief and may be extremely effective in vascular headaches.

When the condition is recognized early in children, the chance for recovery in food allergies, migraine, environmental, and tension headaches are good. It all sums up to evaluating the child and arriving at a diagnosis. Many of our patients after a thorough checkup had diminishing attacks and 38% had complete relief within a three month period; the others are on the way to recovery. Only a small precentage will need guidance, psychiatric consultation, or change of environment to obtain a reasonably good result. Much progress has been made in the past decade in a better understanding and treatment of headache.

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CANCER: A COLLAGEN DISEASE, SECONDARY TO A NUTRITIONAL DEFICIENCY?

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In a previous paper[1] we advanced the hypothesis that the invasive metastasis of cancer was etiologically secondary to a degenerative change in the connective tissues, notably the condensed connective tissue of the "basement membrane" underlining the epithelium of the dermal and mucosal tissues, which in turn could be secondary to a deficiency of vitamin C. This same deficiency could involve the collagenous intercellular cement substance which normally holds the epithelial cells together in orderly arrangement, thus further contributing to faulty healing and metastasis of precancerous lesions.

Since our first paper on this subject was published, additional evidence contributory to the validity of our hypothesis has come to our attention, which we wish to present.

Gillman et al.[2], in a histopathological study of dermal injuries, report that 1) The dermal changes in chronically injured areas seem to represent either alterations in pre-existing collagen or elastin, resulting in the formation of "pseudo-elastic tissue", definable by both morphologic and tinctorial criteria". *2*) This pseudo-elastic tissue is regularly encountered in sites of chronic injury to connective tissues in the skin, as well as in other structures such as the arteries and gall bladder. 3) This pseudo-elastic tissue, preceded by and associated with extensive, though non-malignant, epidermal invasion of the dermis, can consistently be produced experimentally in normal human subjects, with altered connective tissue in injured sites. In their summary these authors state: 1) "It is shown that similar elastotic degeneration of collagen is invariably present in the dermis in many degenerative skin conditions which may and frequently do become precancerous. *2*) It is suggested that the elastotically degenerated dermal collagen may play an important role in the pathogenesis of skin cancer." These authors in no way implicated vitamin-C status as related to the development of the elastotic degeneration of collagen observed in their experiments, and no determination of the vitamin-C status of their subjects was reported.

The observations of Gillman et al. are not altogether new. Bonney[3], in a study of precancerous tissue changes, finds constant

loss of connective tissue, usually hyaline changes in the collagen and fraying at the edges of epithelial cells. He states: "In the area of primary carcinoma there has always occurred a complete disappearance of yellow elastic tissue, and it is in this de-elasticized area that the first epithelial down-growths occur." (Bonney, in 1908, had no knowledge of vitamin C.)

Wolbach, S. B. and Howe, P. R.[4] have observed that the ground substance (collagen), normally effective as an intercellular cement substance, capable of holding epithelial cells together in normal relationship, assumes a watery consistency in scurvy. Gersh, I. and Catchpole, H. R.[5] found that the liquefaction of collagen in scurvy is a depolymerization of glycoprotein, the major constituent of the normal ground substance. Pirani, C. L. and Catchpole, H. R.[6] found that the glycoprotein thus liquified is released into the blood stream, resulting in an increased serum level of same. Wolbach, S. B.[7] found that administration of ascorbic acid (vitamin C) in scurvy rapidly restores the normal consistency of collagen. Simpkin, S. et al.[8] report that an increase of serum glycoprotein is found in cancer, and other studies by Wingler, 1953, Greenspan, 1954, Locky et al., 1956, and Lansing, 1957, have confirmed this finding. A correlation of these findings gives definite support to our hypothesis. As further evidence a diagnostic test for cancer has been developed in Germany (The Whitting Reaction) based on the blood protein picture.[9]

Schneider, E.[10] cites Eickhorn as finding a pronounced deficiency of vitamin C in cancer cases, averaging 4,550 mg. by the saturation method, while his non-cancerous controls averaged only 1,3550 mg. Bodansky et al.[11] studied the vitamin-C level of blood plasma and white blood cells in healthy subjects as compared to that of cancer cases. They found the levels in the latter to be significantly lower. Russell et al.[12] report that recurrent periods of scurvy, interspersed with periods of lettuce supplementation to prevent death, resulted in a significant shortening of the time of appearance of induced cancer in guinea pigs. These findings give further support to the etiologic relationship of vitamin-C deficiency in cancer.

In accordance with the above observations we maintain that the degree of malignancy is determined inversely by the degree of connective-tissue resistance, which in turn is dependent upon the adequacy of vitamin-C status. To illustrate this point, the scirrhus or hard cancer of the breast is slow to metastasize and may remain inactive, or "in situ", for many years; whereas the medullary or

soft cancer of the breast is extremely invasive. In the former there is predominant connective-tissue stroma which binds the cells together more effectively, while in the latter the structure is mainly cellular and almost completely lacking in connective-tissue support. It may be that cancer cells, which are known to assume amoeboid activity, do so because of an inherent propensity, which becomes manifest solely because they have lost their connective-tissue anchorage as a direct result of vitamin-C deficiency. Furthermore, the efficacy of the Papanicolaou and other diagnostic smear tests may be solely due to this same loosely-bound and easy-shedding property of cancer cells that have thus lost their anchorage. The teeth become loose in scurvy for the same reason, namely the liquefaction of the cementum which normally holds them in their sockets under adequate vitamin-C status.

That the cancer cell, per se, is not malignant is shown by the fact that even after metastasis to distant parts of the organism it continues to exercise in degree its normal genetic function. For instance, secondary breast tumors have been found to secrete milk, secondary gastric tumors to secrete hydrochloric acid and pepsin, secondary liver tumors to secrete bile, etc.

The systemic or metabolic nature is shown by the recorded occurrence of multiple primary cancers (3.7% of all cases according to U. S. statistics). In 420 such cases reported by Warren and Gates 111 had 3 or more primary lesions, 67 had primary cancer in symmetrical organs, and 242 had primary cancer in different organs. We have recently seen reports of 2 cases in which 5 primary cancers were found. If our hypothesis is valid it would appear that the term "malignant disease" is a misnomer. Cancer is not a disease that strikes its victims like a bolt of lightning from a clear sky, but rather an ailment that we unwittingly cultivate or contract by perverse habits of life. Ravdin, I. S.[13] has said: "While surgery and radiology are helpful, they do not attack the underlying biological defects. . . . Some time, some place, the existing jigsaw puzzle will be properly put together, and we shall wonder why the correct answer evaded us for so long a time."

The therapeutic implications from the above observations suggest that our major effort should be directed toward prevention of the cause of the cellular disarrangement—collagenous breakdown of epithelial and sub-epithelial tissues—as manifested in open sores or fissures that fail to heal readily, and unusual or easily produced hemorrhage, since such lesions may readily become precancerous. Advance warning of such conditions may be noted in

female subjects who bruise easily, as indicated by unaccountable "black and blue" marks. We have found that fully 90% of our adult female population are so afflicted, yet little or nothing is done about it, although this condition can be readily reversed in a matter of days by a liberal intake of vitamin C from natural sources, supplemented by oral or parenteral ascorbic acid in pronounced cases.

Our observations have led us to the conclusion that the major cause of vitamin-C deficiency in our modern civilization may be the well-nigh universal tobacco addiction. The smoking habit not only militates against normal nutritional practice, but actually neutralizes or destroys to a great extent what little vitamin C is taken in food. We have found by clinical and laboratory means (in checking the vitamin-C requirements of subjects while smoking and not smoking) that the smoking of one cigarette, as ordinarily inhaled, tends to neutralize in the body about 25 mg. of vitamin C, or the content of an average-sized orange. This reciprocal effect is due to the pronounced chemical action of ascorbic acid as a reducing agent.[11] Our findings in this respect have been confirmed in general by independent research in U. S. A. and in Europe. On the basis of our hypothesis these findings would explain the phenomenal increase in lung cancer in smokers in recent years.

This new theory of the etiological relationship of vitamin-C defiency in cancerogenesis suggests the possibility that all physical and chemical cancerogens may act indirectly by bringing about or exaggerating a latent deficiency of vitamin-C. A comparable situation has prevailed regarding alcohol. For many years it was thought that alcohol was the specific cause of peripheral neuritis in the alcoholic subject, but it is now known that deficiency of vitamin B_1 is the culpable agent, the alcohol acting indirectly by increasing the body requirement of this vitamin.

Recently the Sloan-Kettering Institute[16] reported a series of experimental transplants of live cancer cells in human subjects in an effort to get answers to the following questions: "Why will cancer strike one American in four, and why will the other three not get cancer? What are the differences between the cancer-prone and the cancer free? Why does a tumor smoulder in one human, grow slowly but steadily in another, flame wildly through the body of a third? Why does a cancer—very rarely, but demonstrably—stop growing, melt, disappear in some patients? Why does cancer growth, in other patients, seem at times temporarily checked, and then why does it accelerate again? . . . Is there im-

munity to cancer? If so, is it something that exists in the cancer-free but is lacking—or lost, or destroyed—in the cancer victim? Are there at least partial natural defenses against cancer? Can they be identified, studied, stimulated, increased, created artificially or borrowed to protect the potential cancer victim—or rescue those attacked?"

To begin with they transplanted cancer tissue under the skin of the forearm in 15 advanced cancer cases. In every case the cancer implant "took", grew vigorously, and spread, for periods ranging from 6 weeks to 6 months, before they were removed by surgery. Obviously these subjects were completely lacking in resistance to cancer. For comparison another group of 14 willing subjects (Inmates of Ohio State Penitentiary), normally healthy and cancer-free, were given similar injections of the same stock of cancer cells, and in every case there was an overwhelming defence reaction, and within 4 weeks almost all the cancer tissue had been destroyed.

In these studies no cognizance was given to the nutritional background or living habits of the subjects and no correlation in this respect was envisaged. It is our belief that if such an assessment had been made a better approach to solution of the problem would have been achieved. However, these experiments seem to confirm the concept of a systemic or metabolic etiology in cancer.

It is not expected that our hypothesis, as advanced herein, will lead to a cure for cancer in its advanced or metastatic stages; but the prospects for prophylaxis and the curbing or containing of the disease in its early stages seem most encouraging. As an aid in the solution of this vital problem it is suggested that biochemical studies of vitamin-C status should be made on all middle-aged subjects, and nutritional guidance given accordingly, in the hope of at least effecting prophylaxis of this terrible disease. A simple qualitative color test of the urine is now obtainable for this purpose. After all, "An ounce of prevention is worth a pound of cure".

SUMMARY

We submit herewith additional evidence in support of our previously advanced hypothesis[1] that deficiency of vitamin C, by bringing about disintegration of epithelial and connective tissue relationships, owing to liquefaction of the intercellular cement substance (collagen), results in a breakdown of orderly cellular arrangement, which could be the precursor to metastasis and malignancy.

The recent observations of Gillman et al. on collagen and connective tissue changes in the dermis of chronically injured areas are cited[2], indicating formation of "pseudo-elastic tissue". They suggest that similar collagenous degeneration is invariably found in the dermis in many degenerative skin conditions which frequently become pre-cancerous and frankly cancerous, and that elastotically degenerated dermal collagen may play an important role in the pathogenesis.

These authors in no way implicated vitamin C deficiency in the etiology of these degenerative changes, but we believe that such nutritional deficiency may be the primary cause of precancerous connective-tissue degeneration.

Other authors are cited to show that the increased serum-glycoprotein level in cancer cases, sometimes used as a diagnostic test, could readily be produced by the breakdown of collagen and associated connective tissue, and we believe that it could thus serve as a precursor of metastasis. Thus cancer could be a collagen disease of nutritional etiology.

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Current Literature

Edited by
MICHAEL A. BRESCIA, M.D.

HUEI-LING, W. AND HSIU-YING, S.: Subcutaneous Gangrene in the Newborn. A Report of Twelve Cases. (Chinese Medical Journal, 76:485, May, 1958).

Twelve cases of subcutaneous gangrene of the newborn are reported. This disease has been rarely mentioned in the literature but its incidence seems to have increased in recent years. It is probably due to increased infection caused by resistant strains of Staphylococcus aureus following the wide use of antibiotics. The chief features of this disease are: redness of the skin over the lumbosacral region, back and buttocks, induration of the skin, rapid changing of skin color from red to dark purple over the central part of the lesion, and sensation of a cleavage space underneath the lesion. The lesion progresses rapidly. The treatment is early incision and drainage. Once the diagnosis is established operation must be performed as early as possible. After incision and drainage, the lesion ceases to progress. AUTHOR'S SUMMARY

BYWATERS, E. G. L. AND THOMAS, G. T.: Prevention of Rheumatic Fever Recurrences. (British Medical Journal, 5092:350 Aug. 9, 1958).

Two comparable groups of patients with rheumatic fever were followed for a period of five years. One group of 96, admitted in 1949-50, were given no prophylaxis either in hospital or after discharge. The other, comprising 88 patients admitted in 1951-2, were given 1 gm. of sulphonamide daily in hospital and after discharge. The period of follow-up in the two groups overlapped by two to four years.

The mean incidence of recurrences per patient-year was 5.6% in the unprotected and 1.2% in the protected. There was only small variation from year to year in each group, and no tendency for the recurrence rate to decrease with time. The reasons for the relatively low incidence of recurrences in the unprotected group and other differences between this and American series are discussed. Toxic reactions were few: none were serious. The duration, dosage, and merits of various forms of prophylaxis (sulfonamide, oral penicillin, and long-acting penicillin by intramuscular injection) are discussed. Author's Summary

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